

Title

Progressive multifocal leukoencephalopathy with Behcet's disease: an insight into pathophysiology

Authors

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Sir,

We report a case of Progressive Multifocal Leukoencephalopathy (PML) with Behcet's Disease (BD), post immunomodulatory agents including rituximab and alemtuzumab. We studied our patient's immunological response, contrasting with a cohort (n=27) of relapsing remitting multiple sclerosis (RRMS) patients. A 33 year-old, right-handed, woman with a 10-year prodrome, was diagnosed with BD in 2005. She had one required criterion i.e. recurrent oral ulceration and 3 minor criteria i.e. recurrent genital ulcers, uveitis confirmed by ophthalmology and characteristic skin disease. She had multiple bowel resections; histology showed extensive ulceration with occasional vessels showing vasculitis. After an initial poor response to glucocorticoids, cyclosporine and thalidomide, she obtained partial remission with infliximab. Following an infusion reaction to infliximab, she had etanercept and then adalimumab for a further 10 months with partial disease control. In June 2006, she received four weekly doses of rituximab, and further two doses in 2007, with partial disease control. Meanwhile, she had multiple infections, recurrent acute kidney injury and required enteral and parenteral nutritional supplementation. In June 2007, she received alemtuzumab, 60mg, which led to complete remission of Behcet's disease symptoms. In May 2014, six months after her sixth alemtuzumab dose, she presented with a two-week history of focal neurological symptoms, indicating a left hemisphere pathology. MRI showed white matter signal abnormalities in the subcortical and juxtacortical areas of the left frontal lobe extending into the parietal subcortical white matter (Figure 1A). Cerebrospinal fluid was acellular, with normal constituents, negative cytology, negative fungal and bacterial cultures, negative viral PCRs for CMV, HSV and VZV. JC-virus PCR was

positive in CSF and blood. Repeat imaging three weeks later (Figure 1B) showed progression of white matter changes. Treatment with intravenous immunoglobulin and mirtazapine was ineffective. She passed away two months later. An autopsy was not performed.

Demyelinating lesions in neurological involvement with BD, tend to follow venular anatomy. They are characteristically seen in the parenchyma near the mesodiencephalic junction and alongside long tracts, often with acute contrast enhancement. The distinctive radiological lesions in our patient, with a positive JC-virus PCR, in the appropriate clinical context, fulfill diagnostic criteria for PML [1].

Amongst the treatments in our patient, anti-TNF therapies would confer a very low risk of PML [2]. Rituximab is a low risk drug, with calculated prevalence around 1/30,000, well below the lowest accurately estimable risk of 1/10,000. From 1997 to 2008, 52 patients with lymphoproliferative disorders, 2 with SLE, 1 with rheumatoid arthritis, 1 with immune thrombocytopenia and 1 with autoimmune pancytopenia developed PML after rituximab [3]. Peripheral CD19 cells remain undetectable for at least 4–5 months post rituximab; the timing of B-cell recovery varies from 16 weeks to over 2 years [4].

In our patient, 18 months following the last dose of rituximab and six months after the first course of alemtuzumab, CD19 counts indicated B-cell reconstitution (Supplementary Figure-S1B). However following the subsequent alemtuzumab courses, there was permanent B-cell depletion. This is an anomalous response to alemtuzumab which depletes both B and T-cells, with B-cells returning to greater than baseline values at 33 ± 6 months post-treatment [5]. CD4 T-cells remain depleted for an average of 61 months and CD8 cells for 30 months.

There have been no cases of PML in RRMS on alemtuzumab. 4 other PML cases post-alemtuzumab have been reported with neoplasias.

Interestingly, immune response in alemtuzumab treated RRMS patients differs from that in natalizumab, a high risk PML drug. The most prominent change post-natalizumab is an increase in CD34+ haematopoietic progenitor cells, along with pre-B and B-cells, due to impaired homing/adhesion in secondary lymphoid organs [6]. Also, majority of circulating B-cells post natalizumab are dominated by memory and marginal zone (MZ)-like B-cells thought to facilitate JCV activation [6]; whereas, post alemtuzumab, CD27- naïve B-cells form the majority of reconstituting B-cells (Supplementary Figure-S2E,F). Natalizumab also suppresses serum and CSF IgG and IgM levels over time, with decreased anti-VZV antibody levels documented in post-natalizumab PML cases. Contrastingly, humoral immunity to common viruses remains intact post alemtuzumab [7]. Lee et al [8] report PML in a natalizumab-treated RRMS patient, who had a splenectomy in childhood. The circulating B-cell pool was significantly high in this case and dominated by memory and MZ-like B-cells. Unusually, PML occurred within a year of natalizumab treatment, raising the possibility that the B-cell phenotype played a role in accelerated JCV reactivation.

The lymphopaenia prior to rituximab and subsequent anomalous reconstitution in our patient, may have been a legacy of prior immunosuppressive therapy or indicate an idiosyncratic, innate or acquired immunodeficiency. Lymphocyte phenotyping showed a highly reactive immune system indicated by the subset of CD4 cells (HLADR+), with very poor CD19 cell reconstitution (Supplementary Figure-S1). These abnormal T and B-cell responses may have contributed to the development of PML.

Key message

Host factors play a key role in development of PML after immunomodulatory agents.

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Conflicts of interests

None

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Figure legend

Figure 1

Initial MRI (2A) shows T2/FLAIR signal intensity with corresponding reduced T1 signal (not shown here) intensity in the white matter with deterioration three weeks later (2B).